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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/893,443	06/29/2001	Michael Gmachl	0652.2310001/EKS/SEZ	6378

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EXAMINER

YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 01/29/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/893,443

Applicant(s)

GMACHL ET AL.

Examiner

Christopher H Yaen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 September 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 28-83 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 28-83 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed 9/30/2002 (paper no. 7) is acknowledged and entered into the record. Accordingly, claims 1-27 have been canceled and claims 28-83 are newly added. Therefore, claims 28-83 are pending and examined on the record.

Information Disclosure Statement

2. The Information Disclosure Statement filed 3/22/2002 (paper no. 6) is acknowledged and considered. A signed copy of the IDS is attached hereto.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in EPO on 6/29/2000. It is noted, however, that applicant has not filed a certified copy of the EP00113832.0 application as required by 35 U.S.C. 119(b).

Claim Rejections Withdrawn- 35 USC § 102

4. The rejection of claims 1 and 3-4 under 35 USC 102(b) as being anticipated by Nasmyth *et al* is withdrawn in view of the arguments presented by the applicant.

Claim Rejections Withdrawn- 35 USC § 103

5. The rejection of claims 1-27 under 35 USC 103 (a) as being obvious over Nasmyth K *et al* in view of Kirschner *et al*, Hatfield *et al*, and Gonen *et al* is withdrawn in view of the arguments presented by the applicant.

New Claim Rejections-35 USC § 112, 2nd paragraph

6. Claims 28-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Regarding claims 28, 46, 66, and dependent claims thereof, in the recitation of the phrase "ability to interfere", it is indefinite because this a relative phrase which relates to the degree of interference of the test compound.

8. Claims 28-83 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how the identification is to take place. It is not clear from the limitations set forth in claims 28, 46, and 66 how a compound is to be identified if there is a lack of essential components that are required for the reaction to take place, such as the presence of E1, E2, and ATP (i.e. how does the ubiquitination reaction take place in the absence of essential components?)

New Claim Rejections-35 USC § 103

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 28-33, 35, 39-41, 46-53, 55, and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirschner *et al* ((WO 96/33286), cited prior office action paper no. 5)) in view of Lorick *et al* (PNAS USA 1999 Sept; 96:11364-11369), Zachariae *et al* (Genes Dev. 1999 Aug;13(16):2039-2058), Gonen *et al* ((J. Biol. Chem. 1999 May;274(21):14823-14830), cited prior office action paper no. 5)), and Hatfield *et al* ((J. Biol. Chem. 1990 Sep;265(26):15813-15817), cited prior office action paper no. 5)). Claims are drawn to a method of identifying a compound that inhibits a ubiquitination reaction comprising the reaction of APC11, ubiquitin, and a test compound or the reaction of APC11, ubiquitin, a substrate, and a test compound,

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followed by the determination of the test compounds ability to inhibit the formation of ubiquitin chains with APC11. The method further comprises the addition of E1, E2 and ATP. The method further limits APC11 to human, E1 to UBA1, E2 to UBCH5b, the measuring of the ubiquitination by an antibody specific for ubiquitin, and the assay components being fused to an affinity tag.

Kirschner *et al* teach an assay for the identification of an inhibitor of ubiquitination reaction, wherein there is the presence of E1, E2, ATP, a substrate, and components of APC (MDC), namely, APC3 (CDC27) and APC6 (CDC16). Kirschner *et al* further disclose a methods of detection of the ubiquitination reaction through the use of an immunoassay and detectable labels on components of the assay system. Kirschner *et al* however, do not specifically teach the use of APC11, nor do they teach the use of specific E1 or E2 enzymes.

Lorick *et al* teach that RING finger containing E3s are vital components to E2-dependent ubiquitination and further suggests that other RING finger containing proteins maybe E3s. Lorick *et al* also point specifically to apc11p (APC11) as an E3 component of APC that contains a RING finger motif. In addition, it is taught that in the absence of RING finger motifs in other E3s, there is a lack of proper ubiquitination reactions, wherein the RING finger motif provides a site of interaction with the E2s.

Zachariae *et al* teach that APC11 is a vital component of the APC system that is involved in the ligation of the E2-ubiquitin to a substrate (see page 2043, figure 2).

Both Gonen *et al* and Hatfield *et al* disclose E2 and E1 enzymes UBCH5b and UBA1 and their involvement in an in vitro ubiquitination process.

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Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screen for inhibitors of ubiquitination using the APC11 subunit of APC, with UBA1 as the E1, UBCH5b as the E2, and ATP and or substrate because Kirschner *et al* taught that the subunits of APC could be used with E1, E2, ATP and or substrate to identify inhibitors of ubiquitination, because Lorick *et al* and Zachariae *et al* taught that RING finger motifs are vital components for the interaction of E2s with E3s, and that specifically APC11 was the only known and identified RING finger containing APC subunit, and because the use of UBA1 and UBCH5b were already known and readily used in the art for in vitro assays for the study of ubiquitination reactions. One of skill in the art would have been motivated to combine the references because RING finger motifs were shown to be important for the interaction of E2s with E3s, and that APC11 was both known as the only RING finger containing APC subunit and because Lorick *et al* specifically alluded to it as an E3 component that may play an important role in the interaction of E2s with E3s. Furthermore, Zachariae *et al* specifically teaches that APC11 (as shown in figure 2) is critical to the proper ubiquitination of a substrate. One of ordinary skill in the art would have known from Lorick *et al* and Zachariae *et al* that APC11 was the critical subunit for the E3 complex and knowing from Lorick *et al* in the absence of APC11, a RING finger containing subunit, the ubiquitination of a substrate would not be possible. One of skill in the art would have combined this knowledge with the fact that Kirschner *et al* had already taught that components of the APC system could have been used on their own with other E1, E2, ATP components to screen for inhibitors. And lastly, one of ordinary

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skill in the art would have known that UBA1 and UBCH5b were already known and readily available to use for in vitro assays for ubiquitination reactions. One of ordinary skill in the art could have expected a reasonable amount of success in screening for inhibitors using APC11, UBA1, UBCH5b, ATP, and substrates because the vital components of the APC, namely APC11, was shown to be vital, that the addition of individual APC subunits to screen for inhibitors of ubiquitination was already taught and practiced, and that UBA1 and UBCH5b were readily available to be used in in vitro assays.

Although claims 34, 36-38, 42-45, and 56-65 are not rejected under 35 USC 103 (a), they are not allowed because they depend from claims that read on the prior art.

Conclusion

11. Claims 28-65 are not allowed.

12. Claims 66-83 appear to be free of the art. The closest prior art found is Buschmann T *et al* (Cell 2000 Jun 23;101(7):753-62), wherein it is taught that Mdm2 is an E3 ubiquitin ligase that the RING finger motif plays a role in self ubiquitination.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Christopher Yaen
Art Unit 1642
January 9, 2003



ALI R. SALIMI
PRIMARY EXAMINER